09173821

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(FILE 'HOME' ENTERED AT 16:04:05 ON 05 AUG 1999)

     FILE 'SCISEARCH, MEDLINE, CAPLUS, BIOSIS, CANCERLIT, INPADOC, JAPIO,
     MEDICONF, AGRICOLA' ENTERED AT 16:04:27 ON 05 AUG 1999
L1       121640 S TRANSGENIC
L2        70682 S L1 AND (RAT OR MICE)
L3         3706 S L2 AND (SV40? OR MMTV? OR NEUROFILAMENT OR NF-L)
L4          196 S L3 AND (TGF? OR ERB?)
L5           92 DUP REM L4 (104 DUPLICATES REMOVED)
L6           92 SORT L5 PY
L7           78 S L6 AND (NEURO? OR CANCER OR TUMOR OR MALIGNAN?)
L8           78 SORT L7 PY
                E RUDLAND PHILIP SPENCER/AU
L9          134 S E2
L10           1 S L9 AND L5
L11           7 S E3
L12           7 DUP REM L11 (0 DUPLICATES REMOVED)
L13           7 SORT L12 PY
L14          92 S L5 AND L3
L15          92 S L14 AND (TGF? OR ERB?)
L16          92 DUP REM L15 (0 DUPLICATES REMOVED)
L17          92 SORT L16 PY
L18          11 S L9 AND TRANSGENIC
L19           7 DUP REM L18 (4 DUPLICATES REMOVED)
L20           7 SORT L19 PY
L21         367 S (NEUROFILAMENT OR NF-L) AND PROMOTER
L22         156 S L21 AND TRANSGENIC
L23          20 S L22 AND (SV40? OR T-ANTIGEN)
L24          11 DUP REM L23 (9 DUPLICATES REMOVED)
L25          11 SORT L24 PY

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(FILE 'USPAT' ENTERED AT 13:41:34 ON 05 AUG 1999)
               DEL HIS
L1         3365 S TRANSGENIC
L2         1177 S L1 AND SV40?
L3          124 S L2 AND MMTV
L4            7 S L2 AND NF(W)L
L5           14 S L3 AND ERB?
L6           14 SORT L5 PD
L7           51 S L3 AND NEURON?
L8           12 S L7 AND NF?
L9           12 SORT L8 PD
L10         303 S L1 AND CELL CYCLE
L11          71 S L10 AND TGF?
L12          25 S L3 AND TGF?
L13          25 SORT L12 PD
L14         556 S L2 AND (MAMMARY OR BREAST)
L15         449 S L14 AND CANCER
L16          54 S L15 AND MMTV
L17          14 S L16 AND ERB?
L18          14 SORT L17 PD
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16. 5,866,759, Feb. 2, 1999, **Transgenic** mice expressing TSSV40 large T antigen; Parmjit Singh Jat, et al., 800/18; 435/354 [IMAGE AVAILABLE]

US PAT NO: 5,866,759 [IMAGE AVAILABLE] L7: 16 of 26
DATE FILED: Jul. 2, 1997

ABSTRACT:
The provision of cell lines from virtually any cell type of the animal body is greatly facilitated by **transgenic** non-human eukaryotic animals of the invention in which at least some cells have (i) a differentiation inhibiting sequence chromosomally incorporated under the control of a non-constitutive promotor and/or (ii) a differentiation inhibiting sequence which is itself conditionally active. Said genes are chromosomally incorporated under the control of a promotor such that expression of said sequence is normally held below an effective level, thus allowing normal cell development. However, cells taken from said animal may be prevented from completing differentiation to a non-dividing state in tissue culture by activating expression of said sequence.

9. 5,773,290, Jun. 30, 1998, Mammary gland-specific promoters; Michael N. Gould, et al., 435/320.1; 536/24.1 [IMAGE AVAILABLE]

US PAT NO: 5,773,290 [IMAGE AVAILABLE] L6: 9 of 14
DATE FILED: Oct. 7, 1996

ABSTRACT:
An isolated DNA fragment comprising a mammary gland-specific promoter is disclosed. Preferably, this promoter promotes gene expression throughout the estrous cycle in a constant manner. In one embodiment, the promoter comprises nucleotides 1154 through 2967 of SEQ ID NO:1 or 1102 through 2910 of SEQ ID NO:2.

3. 5,455,164, Oct. 3, 1995, Ruminant immortalized mammary epithelial cell lines; Jeffrey D. Turner, 435/6, 69.1, 325, 948 [IMAGE AVAILABLE]

US PAT NO: 5,455,164 [IMAGE AVAILABLE] L6: 3 of 14
DATE FILED: Apr. 30, 1993

ABSTRACT:
The present invention relates to a ruminant immortalized mammary epithelial cell line which has normal physiological responses in that it produces milk constituents which comprises .alpha. and .beta.-casein and lactose. There is provided, using the cell line of the present invention a method in vitro studying lactation. There is provided a method of in vitro screening for gene expression of DNA constructs for **transgenic** ruminant animals. The cell line can be further used in a method for expressing foreign genes. One cell line of the present invention has been deposited at the ATCC under the accession number CRL10274.

1. 4,736,866, Apr. 12, 1988, **Transgenic** non-human mammals; Philip Leder, et al., 800/10; 435/6, 317.1; 536/23.5; 800/18 [IMAGE AVAILABLE]

US PAT NO: 4,736,866 [IMAGE AVAILABLE] L6: 1 of 14
DATE FILED: Jun. 22, 1984

ABSTRACT:
A **transgenic** non-human eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage.

2. 5,087,571, Feb. 11, 1992, Method for providing a cell culture from a **transgenic** non-human mammal; Philip Leder, et al., 435/354; 800/25 [IMAGE AVAILABLE]

US PAT NO: 5,087,571 [IMAGE AVAILABLE] L6: 2 of 14
DATE FILED: Mar. 22, 1988

ABSTRACT:
A **transgenic** non-human eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage.

25. 5,919,997, Jul. 6, 1999, **Transgenic** mice having modified cell-cycle regulation; David H. Beach, et al., 800/18; 435/91.2, 320.1, 325, 455, 463, 467; 800/3, 22, 25 [IMAGE AVAILABLE]

US PAT NO: 5,919,997 [IMAGE AVAILABLE] L13: 25 of 25
DATE FILED: Apr. 4, 1996

ABSTRACT:
The present invention relates to **transgenic** mice in which the biological function of at least one cell cycle regulatory proteins of the INK4 family is altered.

9. 5,773,290, Jun. 30, 1998, **Mammary** gland-specific promoters; Michael N. Gould, et al., 435/320.1; 536/24.1 [IMAGE AVAILABLE]

US PAT NO: 5,773,290 [IMAGE AVAILABLE] L18: 9 of 14
DATE FILED: Oct. 7, 1996

ABSTRACT:
An isolated DNA fragment comprising a **mammary** gland-specific promoter is disclosed. Preferably, this promoter promotes gene expression throughout the estrous cycle in a constant manner. In one embodiment, the promoter comprises nucleotides 1154 through 2967 of SEQ ID NO:1 or 1102 through 2910 of SEQ ID NO:2.

2. 5,087,571, Feb. 11, 1992, Method for providing a cell culture from a **transgenic non-human mammal; Philip Leder, et al., 435/354; 800/25 [IMAGE AVAILABLE]**

US PAT NO: 5,087,571 [IMAGE AVAILABLE] L18: 2 of 14
DATE FILED: Mar. 22, 1988

ABSTRACT:
A **transgenic** non-human eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage.

8 ANSWER 37 OF 78 SCISEARCH COPYRIGHT 1999 ISI (R)
TI AN INBRED COLONY OF ONCOGENE ***TRANSGENIC*** ***MICE*** - DIVERSITY OF ***TUMORS*** AND POTENTIAL AS A THERAPEUTIC MODEL
SO BRITISH JOURNAL OF CANCER, (JAN 1996) Vol. 73, No. 1, pp. 65-72. ISSN: 0007-0920.
AU THOMAS H; HANBY A M; SMITH R A; HAGGER P; PATEL K; RAIKUNDALIA B; CAMPLEJOHN R S; BALKWILL F R (Reprint)
AB ***Transgenic*** ***mice*** carrying the activated ***rat*** c-neu oncogene under transcriptional control of the ***MMTV*** promoter were backcrossed to BALB/c ***mice*** , with the aim of developing a model for ***cancer*** therapy. A total of 86 of 268 transgene-positive ***mice*** in the first five generations developed 93 histologically diverse tumours (median age of onset 18 months). The cumulative incidence of breast tumours at 24 months was 18%, and overall tumour incidence 31%. As well as expected c-neu expressing breast ***cancers*** , lymphomas and Harderian gland carcinomas developed. Virgin ***mice*** had fewer mammary tumours than those with two litters. Breast carcinomas metastasised to the lungs, and lymphomas were widely disseminated. The tumours showed a range of architectural patterns, which resembled human breast ***cancers*** or lymphomas. This diversity was reflected in S-phase fraction and aneuploidy. Breast tumours transplanted to nude ***mice*** showed variable responses to interferon (IFN)-alpha and gamma. A tumour transplanted to BALB/c ***mice*** responded to interleukin (IL)-12. There was significant decline in transgene positivity with successive generations. The diversity, histological and biological resemblance to human ***cancer*** suggests that the model has potential for evaluating novel therapies. However, further genetic and environmental manipulations are required to increase tumour incidence and decrease age of onset.

L8 ANSWER 35 OF 78 SCISEARCH COPYRIGHT 1999 ISI (R)
TI NDF/HEREGULIN INDUCES PERSISTENCE OF TERMINAL END BUDS AND ADENOCARCINOMAS IN THE MAMMARY-GLANDS OF ***TRANSGENIC*** ***MICE***
SO ONCOGENE, (18 APR 1996) Vol. 12, No. 8, pp. 1781-1788. ISSN: 0950-9232.
AU KRANE I M; LEDER P (Reprint)
AB Neu differentiation factor (NDF), a member of the neuregulin family of ligands of ***erbB*** receptors, induces both differentiative and mitogenic effects on cultured human mammary epithelial cells, Since members of the epidermal growth factor receptor family, including Neu/ ***erbB2*** , have been implicated in mammary carcinoma, we wished to know whether a potential ligand of this family, NDF, could induce such effects in the mammary gland in vivo, We therefore targeted expression of NDF to the mammary gland of ***transgenic*** ***mice*** using the mouse mammary ***tumor*** virus (***MMTV***) promoter in a fusion a clear, but subtle effect on adult virgin gland of female ***transgenic*** animals, Terminal end bud structures (TEBs), which normally disappear from the mammary gland at the age of similar to 8 weeks in wild type ***mice*** , persist in glands of virgin ***MMTV*** -NDF ***transgenic*** females, suggesting that NDF inhibits signals that normally lead to the terminal differentiation of these structures, Further, female ***mice*** , bred continuously to maximize expression of the transgene in the mammary gland,develop mammary adenocarcinomas at a median age of 12 months, Since these ***tumors*** arise in a solitary fashion, we infer that NDF is necessary, but not sufficient for their formation, In order to explore the signal transduction pathways potentially activated by NDF, we examined expression of the receptors ***erbB2*** , ***erbB3*** and ***erbB4*** in mammary epithelial

cells established from induced ***tumor*** , All three receptors were though only the ***erbB3*** receptor was phosphorylated, suggesting that overexpression of NDF might operate through this receptor, Additionally, about 50% of ***MMTV*** -NDF ***transgenic*** ***mice*** developed Harderian (lachrymal) gland hyperplasia, a benign ***tumor*** that does not progress to frank malignacy.

L8 ANSWER 33 OF 78 CANCERLIT
TI Mammary gland development in ***transgenic*** ***mice*** expressing a dominant-negative transforming growth factor-beta type II receptor under the control of the mouse mammary ***tumor*** virus promoter/enhancer (Meeting abstract).
SO Proc Annu Meet Am Assoc Cancer Res, (1995). Vol. 36, pp. A1119. ISSN: 0197-016X.
AU Gorska A E; Serra R; Chen R H; Derynck R; Moses H L
AB We are interested in the transforming growth factor beta (***TGF*** beta) signaling pathway and its implications in development and carcinogenesis. This project is focused on the role of ***TGFbeta*** in mouse mammary gland development. The role of ***TGFbeta*** has been studied in ***transgenic*** ***mice*** expressing a dominant-negative ***TGFbeta*** type II receptor (DN beta II) under the control of the mouse mammary ***tumor*** virus (***MMTV***) promoter/enhancer, which directs expression to the mammary gland. The dominant-negative mutant acts to block signaling through the ***TGF*** beta type II receptor. Previous data have shown that overexpression of constitutively active ***TGFbeta*** I in the mammary gland using ***MMTV*** results in mammary ductal hypoplasia and inhibition of mammary ***tumor*** development. In our ***MMTV*** -DN beta IIR ***transgenic*** mouse model, the expression of the transgene leads to mammary epithelial hyperplasia. This effect is observed in 13-week-old females and is more apparent at 20 weeks. Also, as ***transgenic*** female ***mice*** get older (15 to 18 weeks) they can no longer feed their litters. Preliminary experiments with dexamethasone treatment of ***transgenic*** female ***mice*** indicate increased hyperplasia of the ductal tree compared to animals without dexamethasone treatment. Expression of the DN beta IIR was confirmed by the Northern blot analysis. We conclude that endogenous ***TGFbeta*** may play an important role in the mammary gland development.

L8 ANSWER 32 OF 78 CANCERLIT
TI Growth factors and their receptors (Meeting abstract).
SO Proc Annu Meet Am Assoc Cancer Res, (1995). Vol. 36, pp. A649-50. ISSN: 0197-016X.
AU Moses H L
AB In the regulation of cell proliferation, most growth factors (EGF, ***TGF*** alpha, FGF, HGF, PDGF and IGF-I) function to stimulate proliferation (positive growth factors) while a few (***TGF*** -beta1, ***TGF*** -beta2 and ***TGF*** -beta3) generally inhibit proliferation (negative growth factors). In general positive growth factors bind to specific cell surface receptors that are transmembrane tyrosine kinases. With binding of the growth factor to its cognate receptor, there is dimerization, auto-phosphorylation (or cross-phosphorylation on tyrosine residues). The phosphorylated tyrosines serve as docking sites for cytoplasmic enzymes or adaptor molecules. The enzymes become phosphorylated and activated and the adaptor molecules activate ras signaling to activate raf which in turn activates the MAP kinase pathway culminating in the modulation of transcription factors necessary for

initiating progression through the early G1 phase of the cell cycle. Once transit through the cell cycle has begun, passage from one phase of the cell cycle to another in an orderly manner is regulated by cyclins. Cyclins function to activate cyclin-dependent kinases (CDKs). The cyclin/CDK holoenzyme complexes are in turn regulated by newly described inhibitors such as p21WAF1, p27kip1, p16ink4A and p15ink4B. Certain of the ***tumor*** suppressor genes that frequently undergo recessive, inactivating mutations in ***cancer*** are involved in these pathways. For example, p53 regulates expression of p21WAF1, an inhibitor of cyclin E/CDK2 activity which is required for progression from late G1 into S phase. Thus, following DNA damage, p53 can, among other things, inhibit progression prior to DNA replication permitting repair before fixation of the damage as a mutation during S phase. The activity of the retinoblastoma ***tumor*** susceptibility gene product (pRb) is regulated through phosphorylation by cyclin D/CDK4 which is required for late G1 and G1/S progression. Underphosphorylated pRb binds to and inactivates the E2F family of transcription factors. With phosphorylation of pRb by cyclin D/CDK4 and/or cyclin E/CDK2, E2Fs become activated and regulate transcription of genes necessary for DNA replication. The negative growth factors such as the ***TGF*** -betas likely mediate their growth inhibitory action in a manner similar to p53 by causing inhibition of cyclin/CDK activity preventing G1/S progression and causing a late G1 arrest. The ***TGF*** -betas bind to heterodimeric transmembrane receptors with serine-threonine kinase domains in the cytoplasmic region. Signaling following binding of ligand to these receptors is less well understood than with the tyrosine kinase receptors. The ***TGF*** -betas have rapid effects on transcription of many different genes. Depending on the cell type, ***TGF*** -betas can suppress expression or activity of cyclins or CDKs. The ***TGF*** -betas can also induce expression of p15ink4B which in turn inhibits cyclin D/CDK4 activity preventing phosphorylation of pRb and the resultant activation of E2F transcription factors. The E2Fs are thought to regulate expression of many genes, including c-myc necessary for G1/S cell cycle progression. Evidence has been presented indicating that ***TGF*** -beta1 suppression of c-myc expression is important in the mechanism of growth inhibition. ***TGF*** -alpha overexpressed in the mammary gland of ***mice*** under control of the ***MMTV*** promoter causes mammary ductal hyperplasia, hyperplastic alveolar outgrowths, and a marked increase in mammary carcinomas. These results are similar to that observed with ***MMTV*** -driven overexpression of oncogenes. In contrast, overexpression of ***TGF*** -beta1 under control of ***MMTV*** causes mammary ductal hypoplasia and no increase in mammary ***tumor*** formation. In crossbreeding experiments involving the derivation of offspring expressing both ***TGF*** -alpha and ***TGF*** -beta1 transgenes, ***TGF*** -beta1 was found to markedly suppress mammary ***tumor*** formation induced by the ***TGF*** -alpha transgene in female ***mice*** . Further, ***MMTV*** - ***TGF*** -beta1 female ***transgenic*** ***mice*** were found to be markedly resistant to induction of mammary ***tumors*** by the chemical carcinogen, (ABSTRACT TRUNCATED)

L8 ANSWER 33 OF 78 CANCERLIT

TI Mammary gland development in ***transgenic*** ***mice*** expressing a dominant-negative transforming growth factor-beta type II receptor under the control of the mouse mammary ***tumor*** virus promoter/enhancer (Meeting abstract).

SO Proc Annu Meet Am Assoc Cancer Res, (1995). Vol. 36, pp. A1119. ISSN: 0197-016X.

AU Gorska A E; Serra R; Chen R H; Derynck R; Moses H L

AB We are interested in the transforming growth factor beta (***TGF*** beta) signaling pathway and its implications in development and carcinogenesis. This project is focused on the role of ***TGFbeta*** in mouse mammary gland development. The role of ***TGFbeta*** has been studied in ***transgenic*** ***mice*** expressing a dominant-negative ***TGFbeta*** type II receptor (DN beta II) under the control of the mouse mammary ***tumor*** virus (***MMTV***) promoter/enhancer, which directs expression to the mammary gland. The dominant-negative mutant acts to block signaling through the ***TGF*** beta type II receptor. Previous data have shown that overexpression of constitutively active ***TGFbeta*** I in the mammary gland using ***MMTV*** results in mammary ductal hypoplasia and inhibition of mammary ***tumor*** development. In our ***MMTV*** -DN beta IIR ***transgenic*** mouse model, the expression of the transgene leads to mammary epithelial hyperplasia. This effect is observed in 13-week-old females and is more apparent at 20 weeks. Also, as ***transgenic*** female ***mice*** get older (15 to 18 weeks) they can no longer feed their litters. Preliminary experiments with dexamethasone treatment of ***transgenic*** female ***mice*** indicate increased hyperplasia of the ductal tree compared to animals without dexamethasone treatment. Expression of the DN beta IIR was confirmed by the Northern blot analysis. We conclude that endogenous ***TGFbeta*** may play an important role in the mammary gland development.

L8 ANSWER 31 OF 78 CANCERLIT

TI The interaction of transforming growth factor alpha and c-myc in mouse mammary gland tumorigenesis (Meeting abstract).

SO J Cell Biochem, (1995). Suppl. 19A, pp. 66.
ISSN: 0730-2312.

AU Amundadottir L T; Johnson M D; Smith G H; Merlino G; Dickson R B

AB Transforming growth factor alpha (***TGFa***) binds to and activates the epidermal growth factor receptor (EGFR). Expression of ***TGFa*** is most predominantly found in transformed cell lines and ***tumors*** of epithelial origin, including breast ***tumors*** . The c-myc proto-oncogene is found amplified in about 30% of breast ***cancer*** . Both c-myc and ***TGFa*** are known to be induced by ovarian hormones in breast ***cancer*** . In various cell types in vitro, overexpression of c-myc results in increased responsiveness to the effects of mitogenic growth factors, including ***TGFa*** . We are exploring the interaction of Myc and ***TGFa*** in vivo in mouse mammary gland tumorigenesis. We mated a ***transgenic*** mouse strain heterozygous for ***TGFa*** (MT100) to a strain heterozygous for Myc (***MMTV*** -cmyc) to yield double ***transgenic*** offspring for ***TGFa*** and Myc. All (20/20) ***TGFa*** /Myc animals developed multiple mammary ***tumors*** at a mean age of 66 days. No single ***transgenic*** ***TGFa*** virgin ***mice*** or wild-type ***mice*** have developed ***tumors*** , but single ***transgenic*** Myc virgin females developed adenocarcinomas of the mammary gland after a long latency time of 9-12 months. An interesting finding was that female and male double ***transgenic*** animals develop mammary gland ***tumors*** with identical latency and frequency, suggesting the ***tumors*** could be estrogen independent. All ***tumors*** are classified as adenocarcinomas type A and B that are locally invasive and have been established in nude ***mice*** . Of other organs that co-express ***TGFa*** and Myc in double ***transgenic*** ***mice*** , salivary glands show abnormalities ranging from ductule hyperplasia to adenocarcinomas. Salivary glands of single

transgenic animals showed minimal ductule hyperplasia (***TGFa*** ***mice***) or no abnormalities (Myc ***mice*** and wild-type ***mice***). In summary, ***TGFa*** and c-myc are powerful, synergistic-acting genes in breast tumorigenesis. Data will also be presented on cyclin overexpression in the ***tumors*** and on characterization of epithelial cell lines from ***TGFa*** /Myc, ***TGFa*** and Myc ***tumors*** .

L8 ANSWER 28 OF 78 MEDLINE

TI **Local regression of breast ***tumors*** following intramammary ganciclovir administration in double ***transgenic*** ***mice*** expressing neu oncogene and herpes simplex virus thymidine kinase.**

SO GENE THERAPY, (1995 Sep) 2 (7) 493-7.
Journal code: CCE. ISSN: 0969-7128.

AU Sacco M G; Mangiarini L; Villa A; Macchi P; Barbieri O; Sacchi M C; Monteggia E; Fasolo V; Vezzoni P; Clerici L

AB Females from a mouse lineage ***transgenic*** for the activated ***rat*** neu oncogene under the control of the mouse mammary ***tumor*** virus (***MMTV***) long terminal repeat (LTR) all develop breast ***tumors*** with high reproducibility within the first 2-3 months of life. These animals were crossed with ***mice*** from a lineage ***transgenic*** for the herpes simplex virus thymidine kinase gene (HSVtk) under the control of its own promoter and polyoma enhancer. Double ***transgenic*** ***mice*** (for both neu and tk) developed breast neoplasias with the same kinetics as the neu-only ***mice*** . ***Tumor*** -bearing double ***transgenic*** ***mice*** , treated intratumorally with the antiviral agent ganciclovir (GCV), showed an inhibiting effect on ***tumor*** growth. However, this effect was not seen either on GCV-treated neu-only ***transgenic*** ***mice*** or on saline-injected controls. This suggests that tk-engineered breast ***tumors*** are susceptible to GCV administered locally, and implies that neu- ***mice*** could be a useful model for testing the effectiveness of HSVtk-bearing vectors followed by systemic GCV on breast ***cancer*** cells.

L8 ANSWER 22 OF 78 CANCERLIT

TI ***TGF*** beta in epithelial proliferation and carcinogenesis (Meeting abstract).

SO Br J Cancer, (1994). Vol. 69, Suppl. 21, pp. 1.
ISSN: 0007-0920.

AU Moses H L

AB The transforming growth factor betas (***TGF*** betas), are potent inhibitors of cell proliferation and are usually secreted in a latent form. ***TGF*** beta 1, ***TGF*** beta 2, and ***TGF*** beta 3 are expressed in distinct but overlapping patterns in most tissues. All three ***TGF*** beta isoforms are potent inhibitors of cell proliferation in vitro and in vivo. The mechanisms of ***TGF*** beta growth inhibition have been investigated. In skin keratinocytes, ***TGF*** beta 1 rapidly suppresses c-myc expression at the level of transcriptional initiation and expression of c-myc was shown to be necessary for proliferation of these cells. Overexpression of c-myc using an inducible construct blocks growth inhibition by ***TGF*** beta 1. In 11.5 day pc lung bud organ cultures, ***TGF*** beta 1 inhibits tracheobronchial epithelial development including branching morphogenesis. The tracheobronchial epithelia express N-myc but not c-myc at this stage of development. ***TGF*** beta 1 was shown to markedly inhibit N-myc expression in epithelia of the lung bud organ cultures and N-myc gene knockout experiments by others have shown that N-myc is required for branching morphogenesis of the tracheobronchial tree. The data indicate

that suppression of expression of either N-myc or c-myc may play a role in ***TGF*** beta growth inhibition. To study the role of ***TGF*** beta 1 in normal mammary development and in mammary neoplasia, we have generated three ***transgenic*** mouse lines that express a simian ***TGF*** beta 1S223/225 mutated to produce a constitutively active product under the control of the ***MMTV*** enhancer/promoter. Expression of the transgene was associated with marked suppression of the normal pattern of mammary ductal tree development in female ***transgenics*** from all three lines. However, during pregnancy, alveolar outgrowths developed from the hypoplastic ductal tree, and lactation occurred. Unlike many other ***transgenic*** mouse models in which expression of ***TGF*** alpha or oncogenes under control of the ***MMTV*** promoter leads to mammary epithelial hyperplasia and increased ***tumor*** formation, the ***MMTV*** - ***TGF*** beta 1 transgene causes conditional hypoplasia of the mammary ductal tree and no spontaneous ***tumors*** have been detected in the ***MMTV*** - ***TGF*** beta 1 ***transgenic*** animals. Crossbreeding of ***MMTV*** - ***TGF*** alpha and ***MMTV*** - ***TGF*** beta 1 ***transgenic*** ***mice*** have shown that expression of the ***TGF*** -beta 1 transgene prevents the increased carcinoma development caused by expression of the ***TGF*** alpha transgene indicating that ***TGF*** beta 1 can inhibit at least the early stages of carcinogenesis. Other studies have shown that overexpression of ***TGF*** beta 1 in carcinoma cells enhances tumorigenicity and metastatic spread. We propose that ***TGF*** beta has a bifunctional role in carcinogenesis retarding carcinoma development but enhancing progression once neoplastic transformation has occurred and the growth inhibitory response to ***TGF*** beta has been lost.

L8 ANSWER 21 OF 78 CAPLUS COPYRIGHT 1999 ACS
TI Human and mouse ***TGF*** .alpha. (hTGF.alpha. and mTGF.alpha.) and mammary gland growth in relation to hormones
SO Proc. Int. Cancer Congr., Free Pap. Posters, 16th (1994), Volume 1, 627-631. Editor(s): Rao, R. S. Publisher: Monduzzi Editore, Bologna, Italy.
CODEN: 62UYAO
AU Mizuno, M.; Harigaya, T.; Nagasawa, H.
AB ***Transgenic*** (Tg) female ***mice*** , in which hTGF.alpha. gene was expressed under the control of mouse mammary ***tumor*** virus (***MMTV***) enhancer/promoter, showed a stimulated normal and neoplastic mammary gland growth. These Tg ***mice*** differed little from non-Tg ***mice*** in the pattern of estrous cycle and serum prolactin (PRL) level. However, Tg mouse minimally increased mammary gland PRL receptor level after parturition and failed lactation. Mouse ***TGF*** .alpha. mRNA was modulated by some hormones, but not hTGF.alpha. mRNA. These were not parallel to the mammary gland response to hormones.

L8 ANSWER 20 OF 78 MEDLINE
TI **Normal and neoplastic mammary gland growth in** ***MMTV*** / ***TGF*** alpha ***transgenic*** ***mice*** .
SO IN VIVO, (1994 May-Jun) 8 (3) 263-70.
Journal code: A6F. ISSN: 0258-851X.
AU Mizuno M; Yamamoto K; Sakamoto S; Mori T; Harigaya T; Nagasawa H
AB Biochemical and Dynamic change of mammary glands in different reproductive states were studied in comparison with histological structures in female and male ***transgenic*** ***mice*** bearing human transforming

growth factor alpha (***TGF*** alpha) cDNA under the control of the mouse mammary tumour virus enhancer/promoter. Female and male F1 ***mice*** between SHN female and ***transgenic*** male ***mice*** were divided into ***TGF*** alpha (+) and ***TGF*** alpha (-) groups according to the presence of ***TGF*** alpha gene at approximately 50 days of age. While there was little difference in mammary gland contents of DNA and RNA in females at 2 months of age, both nucleic acid contents were elevated markedly in ***TGF*** alpha (+) female ***mice*** with large variations at 4 months. These extremely high DNA and RNA contents in the ***TGF*** alpha (+) group declined to the level of the ***TGF*** alpha (-) group in the middle of pregnancy and at the end of pregnancy, respectively. Thymidine kinase (TK) activity in the mammary glands as an index of DNA synthesis was significantly higher in ***TGF*** alpha (+) ***mice*** than in ***TGF*** alpha (-) ***mice*** at both 2 and 4 months of age and the high TK in ***TGF*** alpha (+) ***mice*** also declined to the level of ***TGF*** alpha (-) ***mice*** with pregnancy. (ABSTRACT TRUNCATED AT 250 WORDS)

L8 ANSWER 19 OF 78 MEDLINE
TI ***TGF*** beta regulation of cell proliferation.
SO PRINCESS TAKAMATSU SYMPOSIA, (1994) 24 250-63. Ref: 73
Journal code: HHI.
AU Moses H L; Arteaga C L; Alexandrow M G; Dagnino L; Kawabata M; Pierce D F Jr; Serra R
AB The beta-type transforming growth factors (***TGF*** beta) are potent inhibitors of cell proliferation. The mechanisms of ***TGF*** beta growth inhibition have been investigated. In skin keratinocytes, ***TGF*** beta 1 rapidly suppresses c-myc expression at the level of transcriptional initiation, and expression of c-myc was shown to be necessary for proliferation of these cells. Overexpression of c-myc, using an inducible construct, blocks growth inhibition by ***TGF*** beta 1. In 11.5 day p.c. lung bud organ cultures, ***TGF*** beta 1 inhibits tracheobronchial epithelial development, including branching morphogenesis. At this stage of development, the tracheobronchial epithelia express N-myc, but not c-myc, ***TGF*** beta 1 was shown to markedly inhibit N-myc expression in epithelia of the lung bud organ cultures. N-myc gene knockout experiments by others have shown that N-myc is required for branching morphogenesis of the tracheobronchial tree. The data indicate that suppression of expression of either N-myc or c-myc may play a role in ***TGF*** beta growth inhibition. To study the role of ***TGF*** beta 1 in normal mammary development and in mammary neoplasia, we have constructed three ***transgenic*** mouse lines that express a simian ***TGF*** beta 1S223/225 mutated to produce a constitutively active product under the control of the ***MMTV*** enhancer/promoter. Expression of the transgene was associated with marked suppression of the normal pattern of mammary ductal tree development in female ***transgenics*** from all three lines. However, during pregnancy, alveolar outgrowths developed from the hypoplastic ductal tree, and lactation occurred. Unlike many other ***transgenic*** mouse models in which expression of ***TGF*** alpha or oncogenes under control of the ***MMTV*** promoter leads to mammary epithelial hyperplasia and increased ***tumor*** formation, the ***MMTV*** - ***TGF*** beta 1 transgene causes conditional hypoplasia of the mammary ductal tree. No spontaneous ***tumors*** have been detected in the ***MMTV*** - ***TGF*** beta 1 ***transgenic*** animals, indicating that overexpression of ***TGF*** beta 1 in mammary epithelia does not

enhance, and may actually suppress, early stages of carcinoma development. Other studies have shown that overexpression of ***TGF*** beta 1 in carcinoma cells enhances tumorigenicity and metastatic spread. We propose that ***TGF*** beta has a bifunctional role in carcinogenesis, retarding carcinoma development but enhancing progression once neoplastic transformation has occurred and the growth inhibitory response to ***TGF*** beta has been lost.

L8 ANSWER 18 OF 78 CAPLUS COPYRIGHT 1999 ACS
TI Transforming growth factor alpha dramatically enhances oncogene-induced carcinogenesis in ***transgenic*** mouse pancreas and liver
SO Mol. Cell. Biol. (1993), 13(1), 320-30
CODEN: MCEBD4; ISSN: 0270-7306
AU Sandgren, Eric P.; Luetteke, Noreen C.; Qiu, Ting Hu; Palmiter, Richard D.; Brinster, Ralph L.; Lee, David C.
AB To characterize the effect(s) of transforming growth factor alpha (***TGF*** .alpha.) during multistage carcinogenesis, ***tumor*** development was examd. in pancreas and liver of ***transgenic*** ***mice*** that coexpressed ***TGF*** .alpha. with either viral (simian virus 40 T antigens [TAg]) or cellular (c-myc) oncogenes. In pancreas, ***TGF*** .alpha. itself was not oncogenic, but it nevertheless accelerated growth of ***tumors*** induced by either oncogene alone, thereby reducing the host life span. Coexpression of ***TGF*** .alpha. and TAg produced an early synergistic growth response in the entire pancreas, together with the more rapid appearance of preneoplastic foci. Coexpression of ***TGF*** .alpha. and c-myc also accelerated ***tumor*** growth in situ and produced transplantable acinar cell carcinomas whose rate of growth was ***TGF*** .alpha. dependent. In liver, expression of ***TGF*** .alpha. alone increased the incidence of hepatic ***cancer*** in aged ***mice*** . However, coexpression of ***TGF*** .alpha. with c-myc or TAg markedly reduced ***tumor*** latency and accelerated ***tumor*** growth. Expression of the ***TGF*** .alpha. and myc transgenes in hepatic ***tumors*** was induced up to 20-fold relative to expression in surrounding nonneoplastic liver, suggesting that high-level overexpression of these proteins acts as a major stimulus for ***tumor*** development. Finally, in both pancreas and liver, combined expression of ***TGF*** .alpha. and c-myc produced ***tumors*** with a more ***malignant*** (less differentiated) appearance than did expression of c-myc alone, consistent with an influence of ***TGF*** .alpha. upon the morphol. character of c-myc-induced ***tumor*** progression. These findings demonstrate the importance of ***TGF*** .alpha. expression during multistage carcinogenesis in vivo and point to a major role for this growth factor as a potent stimulator of ***tumor*** growth.

L8 ANSWER 17 OF 78 MEDLINE
TI Chemical effects in ***transgenic*** ***mice*** bearing oncogenes expressed in mammary tissue.
SO CARCINOGENESIS, (1993 Jan) 14 (1) 29-35.
Journal code: C9T. ISSN: 0143-3334.
AU Tennant R W; Rao G N; Russfield A; Seilkop S; Braun A G
AB Three ***transgenic*** mouse lines carrying v-Ha-ras (TG-SH), c-myc (TG-M) or c-neu (TG-NK) oncogenes under regulatory control of mouse mammary ***tumor*** virus (***MMTV***) long terminal repeat (LTR) sequences were evaluated for responses to two chemical carcinogens. p-Cresidine, a mutagenic urinary bladder carcinogen, increased the incidence of urinary bladder carcinomas in males and females in all three

lines, and these ***tumors*** occurred at comparable incidences and grade in ***transgenic*** and non- ***transgenic*** ***mice*** . p-Cresidine did not affect the rates of mammary or salivary gland neoplasms in ***transgenic*** ***mice*** ; these ***tumors*** did not occur in non- ***transgenic*** littermates. No other ***tumor*** types were observed in exposed or control animals. Reserpine, a non-mutagenic mammary gland carcinogen, was administered under the same protocol, but the high control rates of mammary gland adenocarcinomas in the TG-M and TG-NK strains made it difficult to detect any ***tumor*** -enhancing effect of reserpine. However, the incidences of multiple mammary gland ***tumors*** were significantly increased in dosed females from both lines. The incidence of mammary gland adenocarcinomas was significantly increased in TG-SH females receiving 5 p.p.m. reserpine. Reserpine did not induce any carcinogenic effects in non- ***transgenic*** ***mice*** . These results indicate that the transcriptional regulation of these three transgenes is a major determinant in the response to p-cresidine and reserpine. The use of ***transgenic*** models for the general detection of carcinogens may require lines in which appropriate genes are targeted for expression in many tissues, or lines in which critical genes have been inactivated.

L8 ANSWER 16 OF 78 SCISEARCH COPYRIGHT 1999 ISI (R)

TI AN ACTIVATED ALLELE OF THE C- ***ERBB* -2 ONCOGENE IMPAIRS KIDNEY AND LUNG-FUNCTION AND CAUSES EARLY DEATH OF ***TRANSGENIC*** ***MICE***

SO JOURNAL OF CELL BIOLOGY, (JUL 1993) Vol. 122, No. 1, pp. 199-208. ISSN: 0021-9525.

AU STOCKLIN E (Reprint); BOTTERI F; GRONER B

AB The pathogenicity of the human c- ***erbB*** -2 oncogene was evaluated in ***transgenic*** ***mice*** . A DNA sequence comprising the promoter-enhancer region of the ***MMTV*** LTR and a constitutively activated allele of the human c- ***erbB*** -2 growth factor receptor gene was introduced into the germ line of ***mice*** . Expression of the transgene was observed in kidney, lung, mammary gland, salivary gland, Harderian gland, and in epithelial cells of the male reproductive tract. All ***transgenic*** ***mice*** expressing the c- ***erbB*** -2 receptor died within four months of birth. Histopathological analysis suggests that preneoplastic lesions in kidney and lung most likely caused organ failure and the early death of the ***transgenic*** ***mice*** . Focal dilatation and atypical proliferation of the tubular epithelial cells was found in the kidney. These hyperplastic lesions were found adjacent to normal tubules.

Immunohistochemistry showed that normal renal structures were completely negative for c- ***erbB*** -2 protein expression. Atypical pseudopapillary proliferation of bronchial and bronchiolar epithelial cells narrowed the bronchial lumen in lung. Alveoli appeared normal. The expression of c- ***erbB*** -2 protein was strictly limited to the proliferating epithelial cells and not detected in normal tissue. The mammary glands of two parous ***mice*** were underdeveloped, lacking lobular-alveolar structures and were lactation deficient. Only a few ducts were interspersed in the fat pad. A virgin mouse developed a focal adenocarcinoma infiltrating the mammary fat pad. Expression of the c- ***erbB*** -2 protein was enhanced in the proliferating epithelial cells.

Transgenic males were sterile. Epithelial hyperplasia and hypertrophy in the epididymis, vas deferens and seminal vesicles was found. The transgene is not uniformly expressed in the tissues where the ***MMTV*** LTR is transcriptionally active. The scattered transgene expression invariably coincides with epithelial hyperplasia.

L8 ANSWER 13 OF 78 SCISEARCH COPYRIGHT 1999 ISI (R)
TI INHIBITION OF MAMMARY DUCT DEVELOPMENT BUT NOT ALVEOLAR OUTGROWTH DURING PREGNANCY IN ***TRANSGENIC*** ***MICE*** EXPRESSING ACTIVE ***TGF*** -BETA-1
SO GENES & DEVELOPMENT, (DEC 1993) Vol. 7, No. 12A, pp. 2308-2317. ISSN: 0890-9369.
AU PIERCE D F (Reprint); JOHNSON M D; MATSUI Y; ROBINSON S D; GOLD L I; PURCHIO A F; DANIEL C W; HOGAN B L M; MOSES H L
AB The transforming growth factors beta (***TGFs*** -beta) are potent inhibitors of cell proliferation and are usually secreted in a latent form. ***TGF*** -beta1, ***TGF*** -beta2, and ***TGF*** -beta3 are expressed in distinct but overlapping patterns in the developing mouse mammary gland. To study the role of transforming growth factor-beta1 (***TGF*** -beta1) in normal mammary development and in mammary neoplasia, we have constructed three ***transgenic*** mouse lines that express a simian ***TGF*** -beta1S223/225 mutated to produce a constitutively active product under the control of the ***MMTV*** enhancer/promoter. Expression of the transgene, as confirmed by in situ hybridization, immunohistochemistry, and Northern blot analysis, was associated with marked suppression of the normal pattern of mammary ductal tree development in female ***transgenics*** . Reduction in total ductal tree volume was observed at 7 weeks, soon after estrous begins, and was most apparent at 13 weeks, as ductal growth in the normal mammary gland declines. This effect was seen in all three lines. However, during pregnancy, alveolar outgrowths developed from the hypoplastic ductal tree, and lactation occurred, therefore, all ***transgenic*** females could feed full litters. Unlike many other ***transgenic*** mouse models in which expression of growth factors or oncogenes under control of the ***MMTV*** promoter leads to mammary epithelial hyperplasia and increased ***tumor*** formation, the ***MMTV*** - ***TGF*** -beta1S223/225 transgene causes conditional hypoplasia of the mammary ductal tree and no spontaneous ***tumors*** have been detected in the ***MMTV*** - ***TGF*** -beta1S223/225 ***transgenic*** animals.

L8 ANSWER 12 OF 78 SCISEARCH COPYRIGHT 1999 ISI (R)
TI DISTINCTIVE PATTERNS OF HYPERPLASIA IN ***TRANSGENIC*** ***MICE*** WITH MOUSE MAMMARY- ***TUMOR*** VIRUS TRANSFORMING GROWTH FACTOR-ALPHA - CHARACTERIZATION OF MAMMARY-GLAND AND SKIN PROLIFERATIONS
SO AMERICAN JOURNAL OF PATHOLOGY, (MAY 1992) Vol. 140, No. 5, pp. 1131-1146. ISSN: 0002-9440.
AU HALTER S A (Reprint); DEMPSEY P; MATSUI Y; STOKES M K; GRAVESDEAL R; HOGAN B L M; COFFEY R J
AB Eight lines of ***transgenic*** ***mice*** expressing a mouse mammary ***tumor*** virus (***MMTV***) human transforming growth factor-alpha (***TGF*** -alpha) fusion gene were established. Three lines with distinctive phenotypes are presented. All have proliferative changes of the mammary gland. One line has sebaceous gland hyperplasia of the skin. Five histologic patterns of mammary gland hyperplasia based on two of these lines were identified: cystic hyperplasia, solid hyperplasia, dysplasia, adenoma, and adenocarcinoma. Human ***TGF*** -alpha mRNA and protein were produced in all patterns but appeared reduced in solid hyperplasia, dysplasia, and adenocarcinoma. ***TGF*** -alpha immunoreactivity in the mammary tissue, cystic fluid, and serum did not show significant differences; hyperplasia developed in 65% of multiparous ***mice*** and 45% of virgin ***mice*** by 12 months of age. Adenocarcinoma developed in 40% of multiparous ***mice*** and 30% of virgin ***mice*** by 16 months of age. These ***transgenic***

lines may provide useful models of mammary and sebaceous gland hyperplasia analogous to human disease.

L8 ANSWER 9 OF 78 CAPLUS COPYRIGHT 1999 ACS
TI ***Transgenic*** animals and cell lines expressing differentiation-inhibiting functions
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
IN Noble, Mark David; **Jat, Parmjit Singh;** Kioussis, Dimitris
AB ***Transgenic*** animals are produced with germ cells and/or somatic cells contg. a chromosomally integrated differentiation-inhibiting gene under control of a regulatable promoter to prevent expression of the gene to allow normal development are prepd. Precursor cells taken from these ***transgenic*** animals may be prevented from completing differentiation in tissue culture by inducing expression of this gene. In this way, immortalized cells from any tissue of the body may be prepd. ***Transgenic*** ***mice*** contg. a chimeric gene using the H-2Kb gene promoter to drive expression of the gene for a temp. sensitive ***SV40*** large T antigen gene were prepd. The gene can be expressed at 33.degree. in the presence of interferon-.gamma.. Immortalized cell lines were prepd. from fibroblasts, glial cells, pancreatic cells, etc. of these ***mice*** .

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9113150	A1	19910905	WO 1991-GB262	19910220
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
CA 2076345	AA	19910821	CA 1991-2076345	19910220
AU 9173286	A1	19910918	AU 1991-73286	19910220
AU 660604	B2	19950706		
EP 516664	A1	19921209	EP 1991-904013	19910220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05504066	T2	19930701	JP 1991-504077	19910220
US 5688692	A	19971118	US 1993-17320	19930211
AU 9533053	A1	19960111	AU 1995-33053	19951005
AU 676118	B2	19970227		
US 5866759	A	19990202	US 1997-887095	19970702

L8 ANSWER 7 OF 78 BIOSIS COPYRIGHT 1999 BIOSIS
TI DEVELOPMENT OF MAMMARY ADENOCARCINOMA IN ***TRANSGENIC*** ***MICE*** OVEREXPRESSING A ***MMTV*** - ***TGF*** -ALPHA COMPLEMENTARY DNA CONSTRUCT.
SO SYMPOSIUM ON GROWTH AND DIFFERENTIATION FACTORS IN DEVELOPMENT HELD AT THE 19TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, STEAMBOAT SPRINGS, COLORADO, USA, MARCH 31-APRIL 7, 1990. J CELL BIOCHEM SUPPL. (1990) 0 (14 PART E), 78.
CODEN: JCBSD7.
AU MATSUI Y; HALTER S A; HOLT J T; HOGAN B L M; COFFEY R J JR

L8 ANSWER 6 OF 78 MEDLINE
TI **Induction of a variety of ***tumors*** by c- ***erbB2*** and clonal nature of lymphomas even with the mutated gene (Val659----Glu659).**
SO EMBO JOURNAL, (1990 Jan) 9 (1) 181-90.
Journal code: EMB. ISSN: 0261-4189.
AU Suda Y; Aizawa S; Furuta Y; Yagi T; Ikawa Y; Saitoh K; Yamada Y; Toyoshima

K; Yamamoto T
AB The c- ***erbB2*** gene is expressed uniquely in fetal epithelium in vivo and has been suggested to contribute to the development and/or progression of adenocarcinomas in man. In order to assess the oncogenicity of the c- ***erbB2*** gene in vivo, normal c- ***erbB2*** and mutant c- ***erbB2*** encoding glutamic acid instead of valine at position 659 within the transmembrane domain were introduced into ***mice*** under the transcriptional regulatory unit of mouse mammary ***tumor*** virus long terminal repeat (***MMTV*** -LTR) or immunoglobulin enhancer-- ***SV40*** early gene promoter (Ig/Tp). In ***transgenic*** ***mice*** with normal c- ***erbB2*** under ***MMTV*** -LTR, not only adenocarcinomas but also a variety of ***tumors*** including B lymphomas were induced at relatively late onset. Induction of pre-B cell lymphomas with normal c- ***erbB2*** was also observed using the Ig/Tp regulatory unit within 6-10 months in some members of one ***transgenic*** family among seven lines established. In contrast, with the mutant c- ***erbB2*** under the Ig/Tp regulatory unit, the lymphoma was induced neonatally in all members of four ***transgenic*** families among ten lines obtained. However, the immunoglobulin heavy chain gene rearrangement pattern indicated that even with the mutant c- ***erbB2*** the induced lymphomas were clonal.

8 ANSWER 3 OF 78 CANCERLIT
TI GROWTH FACTORS, ONCOGENES, AND BREAST ***CANCER*** .
SO Dev Oncol, (1987). Vol. 51, pp. 155-71.
AU Pawson T
AB The relationship between oncogenes and breast ***cancer*** is reviewed, including oncogene characteristics, oncogene-encoded proteins, the function of proto-oncogenes, the role of proto-oncogenes in cell growth and differentiation, interactions between oncogene proteins, retroviral carcinogenesis, oncogenes in human ***tumors*** , tumorigenesis by mouse mammary ***tumor*** virus (***MMTV***), regulation of ***MMTV*** replication and gene expression, experimental induction of mammary adenocarcinoma by activated oncogenes, activated oncogenes in human breast ***cancer*** cell lines, and steroid hormone receptors as oncogenes. Current evidence strongly suggests that the inappropriate expression of genes normally active in regulating cell proliferation may contribute in a fundamental way to the development of human breast ***cancer*** . Experimental data supporting this hypothesis are as follows: (1) ***MMTV*** activates two putative proto-oncogenes, int-1 and int-2; (2) the c-myc oncogene induces mammary adenocarcinoma in ***transgenic*** ***mice*** ; (3) activation of the c-Ha-ras oncogene by a chemical carcinogen induces breast ***cancer*** in ***rats*** ; (4) human breast ***cancer*** cell lines have amplified or activated ras oncogenes and expression of the mutated ras oncogene is sufficient to relieve the MCF-7 line of its dependence on estrogen for ***tumor*** formation; and (5) the estrogen receptor is related in structure to the known retroviral oncogene, ***erbA*** . At least three general methods for blocking oncogene function can be envisioned: (1) the actions of proto-oncogene products are normally antagonized by a variety of cellular processes; augmenting these negative regulatory pathways might induce reversion; (2) monoclonal antibodies to growth factors responsible for the autocrine stimulation of ***tumor*** cells or to external epitopes of oncogenically active transmembrane receptors might be effective in blocking their action; and (3) agents that biochemically inhibit oncogene products, such as active-site inhibitors or agents that prevent appropriate localization of the transforming protein within the cell, might have potential therapeutic

value. (83 Refs)

*****Rudland, Philip**

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
TI Induction of a variety of preneoplasias and tumors in the mammary glands of ***transgenic*** ***rats***
SO Biochem. Soc. Symp. (1998), 63(Mammary Development and Cancer), 167-184
CODEN: BSSYAT; ISSN: 0067-8694
AU Davies, Barry R.; Warren, Joe R.; Schmidt, Gunter; ***Rudland, Philip*** ***
S.***
AB Although ***transgenic*** mouse models for breast cancer have frequently been reported in the literature, ***transgenic*** ***rat*** models have not been described. The authors have generated ***transgenic*** ***rats*** overexpressing the human transforming growth factor .alpha. (***TGF*** .alpha.) and c- ***erbB*** -2 genes in the mammary gland under the control of the mouse mammary tumor virus (***MMTV***) long terminal repeat promoter, and have analyzed multiple lines of these ***rats*** to the second (F2) generation. Female ***MMTV*** / ***TGF*** .alpha. ***rats*** frequently develop severe hyperplasias during pregnancy, and a variety of tumors of long latency. The mammary glands of ***MMTV*** / ***TGF*** .alpha. ***rats*** fail to involute fully after the completion of lactation. Expression of the ***TGF*** .alpha. transgene is highest in the hyperplasias. ***MMTV*** /c- ***erbB*** -2 female ***rats*** develop a spectrum of benign and malignant lesions, including ductal carcinoma in situ and carcinomas. Expression of the c- ***erbB*** -2 transgene is found in benign tumors such as fibroadenomas, but is highest in the carcinomas. These animals model a spectrum of lesions found in human breasts and suggest that ***TGF*** .alpha. overexpression can act at a relatively early stage in the pathogenesis of breast cancer in the ***rat*** , resulting in a predominantly hyperplastic response, whereas overexpression of c- ***erbB*** -2 plays a role in the induction of various benign lesions and more advanced breast carcinomas.

L13 ANSWER 6 OF 7 CAPLUS COPYRIGHT 1999 ACS
TI Conditionally immortalized cell lines derived from transgenic animals and their toxicological and pharmacological uses
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
IN ***Rudland, Philip Spencer*** ; Barraclough, Barry Roger; Kilty, Iain Charles; Davies, Barry Robert; Schmidt, Guenter
AB Provided is a cell line derived from a transgenic animal comprising (1) a conditional oncogene, transforming gene or immortalizing gene or a cell cycle affecting gene; and (2) a cell type specific promoter. They include a neuronal cell line in which the cell type specific promoter is an NF-L gene promoter, and a mammary cell line in which the cell type specific promoter is a MMTV gene promoter. The conditional oncogene, transforming gene or immortalizing gene is preferably a SV40 tsA58 gene. Prodn. of transgenic Sprague Dawley rats by using mammary-targeting vector MMTVLTRtsA58U19 (contg. MMTV Long Terminal Repeat) or brain-targeting vector NF-LtsA58.delta.t (contg. human neurofilament light chain promoter), and prepn. of cell lines B2LT1 and NF2C from the mammary of MMTVLTRtsA58U19 transgenic rats and the brain of NF-LtsA58.delta.t transgenic rats, resp., were shown. Prodn. of transgenic rats carrying oncogene such as c-erb.beta.-2 or transforming growth factor .alpha.

(TGF.alpha.) that are highly assocd. with breast cancer was also shown. The transgenic animals and their immortalized cell lines are useful for toxicol. and pharmacol. studies.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9739117	A1	19971023	WO 1997-GB1063	19970417
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9725723	A1	19971107	AU 1997-25723	19970417
	EP 904363	A1	19990331	EP 1997-917342	19970417
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

LEVEL 1
AN 46427665 INPADOC EW 199806 UW 199806
TI CONDITIONALLY IMMORTALISED CELL LINES DERIVED FROM TRANSGENIC ANIMALS
IN PHILIP SPENCER RUDLAND; BARRY ROGER BARRACLOUGH; IAIN CHARLES KILTY; BARRY ROBERT DAVIES; GUENTER SCHMIDT
INS ***RUDLAND PHILIP SPENCER*** ; BARRACLOUGH BARRY ROGER; KILTY IAIN CHARLES; DAVIES BARRY ROBERT; SCHMIDT GUENTER
PA THE UNIVERSITY OF LIVERPOOL
PAS UNIV LIVERPOOL
DT Patent
PIT AUA1 COMP. SPEC. OPEN TO PUB. INSP.
PI AU 9725723 A1 19971107
AI AU 1997-25723 A 19970417
PRAI GB 1996-7953 A 19960417
WO 1997-GB1063 W 19970417
ICM (6) C12N015-00
ICS (6) C12N005-10; (6) A01K067-027; (6) G01N033-50; (6) G01N033-68; (6) C12N015-33; (6) C07K014-025; (6) C12N015-12; (6) C07K014-475; (6) C07K014-495

L13 ANSWER 2 OF 7 INPADOC COPYRIGHT 1999 EPO

LEVEL 1
AN 42469927 INPADOC UW 199803
TI CONDITIONALLY IMMORTALISED CELL LINES DERIVED FROM TRANSGENIC ANIMALS
IN RUDLAND, PHILIP, SPENCER; BARRACLOUGH, BARRY, ROGER; KILTY, IAIN, CHARLES; DAVIES, BARRY, ROBERT; SCHMIDT, GUENTER
INS ***RUDLAND PHILIP SPENCER*** ; BARRACLOUGH BARRY ROGER; KILTY IAIN CHARLES; DAVIES BARRY ROBERT; SCHMIDT GUENTER
INA GB; GB; GB; GB; GB
PA THE UNIVERSITY OF LIVERPOOL; RUDLAND, PHILIP, SPENCER; BARRACLOUGH, BARRY, ROGER; KILTY, IAIN, CHARLES; DAVIES, BARRY, ROBERT; SCHMIDT, GUENTER
PAS UNIV LIVERPOOL; RUDLAND PHILIP SPENCER; BARRACLOUGH BARRY ROGER; KILTY IAIN CHARLES; DAVIES BARRY ROBERT; SCHMIDT GUENTER
PAA GB; GB; GB; GB; GB; GB
TL English; French
LA English
DT Patent

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PIT   WOA1 PUBL.OF THE INT.APPL. WITH INT.SEARCH REPORT
PI    WO 9739117          A1 19971023
DS    RW: GH KE LS MW SD SZ UG AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT
          SE BF BJ CF
       W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU
          IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ
          PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN AM AZ BY KG KZ
          MD RU TJ TM
AI    WO 1997-GB1063       A  19970417
PRAI  GB 1996-7953         A  19960417
OSCA  127:355930
OSDW  97-526454
ICM   (6) C12N015-00
ICS   (6) C12N005-10; (6) A01K067-027; (6) G01N033-50;
      (6) G01N033-68
ICA   (6) C12N015-33; (6) C07K014-025; (6) C12N015-12;
      (6) C07K014-475; (6) C07K014-495
EPC   A01K67/027A3C; A01K67/027A3B; C12N5/10

L13   ANSWER 3 OF 7  INPADOC  COPYRIGHT 1999 EPO

LEVEL 1
AN    42251143 INPADOC  UW 199803
TI    METASTASIS INDUCING DNA'S
IN    RUDLAND, PHILIP, SPENCER; BARRACLOUGH, BARRY, ROGER
INS     ***RUDLAND PHILIP SPENCER***  ; BARRACLOUGH BARRY ROGER
INA   GB; GB
PA    THE UNIVERSITY OF LIVERPOOL; RUDLAND, PHILIP, SPENCER; BARRACLOUGH,
      BARRY, ROGER
PAS   UNIV LIVERPOOL; RUDLAND PHILIP SPENCER; BARRACLOUGH BARRY ROGER
PAA   GB; GB; GB
TL    English; French
LA    English
DT    Patent
PIT   WOA1 PUBL.OF THE INT.APPL. WITH INT.SEARCH REPORT
PI    WO 9725443          A1 19970717
DS    RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
       W: JP US
AI    WO 1997-GB74         A  19970110
PRAI  GB 1996-470          A  19960110
OSCA  127:172244
OSDW  97-372878
ICM   (6) C12Q001-68
ICS   (6) C12N015-11
EPC   C12N15/11; C12N15/85; C12Q1/68M6B

L13   ANSWER 4 OF 7  INPADOC  COPYRIGHT 1999 EPO

LEVEL 1
AN    27407379 INPADOC  EW 199913  UW 199913
TI    CONDITIONALLY IMMORTALISED CELL LINES DERIVED FROM TRANSGENIC ANIMALS
IN    RUDLAND, PHILIP, SPENCER; BARRACLOUGH, BARRY, ROGER; KILTY, IAIN,
      CHARLES; DAVIES, BARRY, ROBERT; SCHMIDT, GUENTER
INS     ***RUDLAND PHILIP SPENCER***  ; BARRACLOUGH BARRY ROGER; KILTY IAIN
      CHARLES; DAVIES BARRY ROBERT; SCHMIDT GUENTER
INA   GB; GB; GB; GB; GB
PA    THE UNIVERSITY OF LIVERPOOL
PAS   UNIV LIVERPOOL
PAA   GB
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TL    English; French; German
LA    English
DT    Patent
PIT   EPA1 PUBL. OF APPLICATION WITH SEARCH REPORT
PI    EP 904363            A1 19990331
DS    R:  AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AI    EP 1997-917342       A  19970417
PRAI  WO 1997-GB1063       W  19970417
      GB 1996-7953         A  19960417
ICM   (6) C12N015-00
ICS   (6) C12N005-10; (6) A01K067-027; (6) G01N033-50;
      (6) G01N033-68
ICA   (6) C12N015-33; (6) C07K014-025; (6) C12N015-12;
      (6) C07K014-475; (6) C07K014-495

=> d l13 5 all


L13   ANSWER 5 OF 7  INPADOC  COPYRIGHT 1999 EPO

LEVEL 1
AN    26733667 INPADOC  EW 199844  UW 199844
TI    METASTASIS INDUCING DNA'S
IN    RUDLAND, PHILIP, SPENCER; BARRACLOUGH, BARRY, ROGER
INS     ***RUDLAND PHILIP SPENCER***  ; BARRACLOUGH BARRY ROGER
INA   GB; GB
PA    THE UNIVERSITY OF LIVERPOOL
PAS   UNIV LIVERPOOL
PAA   GB
TL    English; French; German
LA    English
DT    Patent
PIT   EPA1 PUBL. OF APPLICATION WITH SEARCH REPORT
PI    EP 873424            A1 19981028
DS    R:  DE FR GB IT
AI    EP 1997-900323       A  19970110
PRAI  WO 1997-GB74         W  19970110
      GB 1996-470          A  19960110
ICM   (6) C12Q001-68
ICS   (6) C12N015-11

L20   ANSWER 6 OF 7  CAPLUS  COPYRIGHT 1999 ACS
TI    Development of hyperplasias, preneoplasias, and mammary tumors in
      MMTV-c-erbB-2 and MMTV-TGF.alpha.   ***transgenic***   rats
SO    Am. J. Pathol. (1999), 155(1), 303-314
      CODEN: AJPAA4; ISSN: 0002-9440
AU    Davies, Barry R.; Platt-Higgins, Angela M.; Schmidt, Gunter;
***Rudland,***
  ***     Philip S.***
AB    Human cDNAs corresponding to two epidermal growth factor-related products
      that are overex-pressed in human breast cancers, that for c-erbB-2 (HER-2)
      and for transforming growth factor .alpha. (TGF.alpha.), have been cloned
      downstream of the mouse mammary tumor virus (MMTV) long terminal repeat
      promoter and injected into the pronucleus of fertilized oocytes of
      Sprague-Dawley rats to produce   ***transgenic***   offspring. Expression
      of the   ***transgenic***   mRNAs is not detectable in mammary tissue from
      virgin   ***transgenic***   rats but is detected in mammary tissue from
      certain lines of mid-pregnant   ***transgenic***   rats. When two such
      lines of either type of   ***transgenic***   rat are subjected to repeated
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cycles of pregnancy and lactation, they produce, primarily in the mammary glands, extensive pathologies, whereas virgin ***transgenic*** rats produce no such abnormalities. Multiparous ***transgenic*** female offspring from c-erbB-2-expressing lines develop a variety of focal hyperplastic and benign lesions that resemble lesions commonly found in human breasts. These lesions include lobular and ductal hyperplasia, fibroadenoma, cystic expansions, and papillary adenomas. More malignant lesions, including ductal carcinoma in situ and carcinoma, also develop stochastically at low frequency. The mammary glands of ***transgenic*** females invariably fail to involute fully after lactation. Similar phenotypes are obsd. in female MMTV-TGF.alpha. ***transgenic*** rats. In addn., multiparous TGF.alpha.-expressing female ***transgenics*** frequently develop severe pregnancy-dependent lactating hyperplasias as well as residual lobules of hyperplastic secretory epithelium and genuine lactating adenomas after weaning. These ***transgenic*** rat models confirm the conclusions reached in ***transgenic*** mice that overexpression of the c-erbB-2 and TGF.alpha. genes predisposes the mammary gland to stochastic tumor development.

L20 ANSWER 5 OF 7 CAPLUS COPYRIGHT 1999 ACS
TI Induction of a variety of preneoplasias and tumors in the mammary glands of ***transgenic*** rats
SO Biochem. Soc. Symp. (1998), 63(Mammary Development and Cancer), 167-184
CODEN: BSSYAT; ISSN: 0067-8694
AU Davies, Barry R.; Warren, Joe R.; Schmidt, Gunter; ***Rudland, Philip*** *** S.***
AB Although ***transgenic*** mouse models for breast cancer have frequently been reported in the literature, ***transgenic*** rat models have not been described. The authors have generated ***transgenic*** rats overexpressing the human transforming growth factor .alpha. (TGF.alpha.) and c-erbB-2 genes in the mammary gland under the control of the mouse mammary tumor virus (MMTV) long terminal repeat promoter, and have analyzed multiple lines of these rats to the second (F2) generation. Female MMTV/TGF.alpha. rats frequently develop severe hyperplasias during pregnancy, and a variety of tumors of long latency. The mammary glands of MMTV/TGF.alpha. rats fail to involute fully after the completion of lactation. Expression of the TGF.alpha. transgene is highest in the hyperplasias. MMTV/c-erbB-2 female rats develop a spectrum of benign and malignant lesions, including ductal carcinoma in situ and carcinomas. Expression of the c-erbB-2 transgene is found in benign tumors such as fibroadenomas, but is highest in the carcinomas. These animals model a spectrum of lesions found in human breasts and suggest that TGF.alpha. overexpression can act at a relatively early stage in the pathogenesis of breast cancer in the rat, resulting in a predominantly hyperplastic response, whereas overexpression of c-erbB-2 plays a role in the induction of various benign lesions and more advanced breast carcinomas.

L20 ANSWER 3 OF 7 CAPLUS COPYRIGHT 1999 ACS
TI Transcriptional down-regulation of the metastasis-inducing S100A4 (p9Ka) in benign but not in malignant rat mammary epithelial cells by GC-factor
SO J. Biol. Chem. (1997), 272(32), 20283-20290
CODEN: JBCHA3; ISSN: 0021-9258
AU Chen, Dongsheng; Davies, Michael P. A.; ***Rudland, Philip S.*** ; Barraclough, Roger
AB The S100-related calcium-binding protein S100A4 (p9Ka) is expressed at a low level in rat mammary epithelial cells from normal mammary gland and

benign mammary tumors. In ***transgenic*** mice, expressed rat S100A4 transgenes cooperate with the activated c-erbB-2 oncogene, neu, to form metastatic mammary tumors. Elevated levels of S100A4 (p9Ka) in cultured benign rat or mouse mammary epithelial cells are assocd. with the induction of metastatic capability. A cis-acting sequence related to the consensus recognition sequence of GC-factor, 1300 base pairs upstream of the start site of transcription of the rat S100A4 gene, acts as a cis-acting inhibitor of transcription of the S100A4 (p9Ka) gene in a low S100A4 (p9Ka)-expressing benign rat mammary epithelial cell line, but not in highly expressing rat mammary epithelial cell lines. There is an inverse relation between the level of S100A4 (p9Ka) mRNA and the level of GC-factor mRNA in a range of rat mammary cell lines. The results suggest a novel mechanism for regulating the expression of the mRNA encoding an S100 protein.

L25 ANSWER 11 OF 11 CAPLUS COPYRIGHT 1999 ACS
TI Expression of a target gene in ***transgenic*** mammals with 5' flanking sequences of the rat tyrosine hydroxylase gene
SO U.S., 34 pp. Cont. of U.S. Ser. No. 973,032, abandoned.
CODEN: USXXAM
IN Chikaraishi, Dona M.
AB Expression of a target gene or transgene in catecholaminergic cells of a ***transgenic*** mammal is achieved by operably linking to the 5' flanking sequence of a rat tyrosine hydroxylase (TH) gene. In order to efficiently target virtually any target gene in catecholaminergic neuronal cells under the control of the 5'-flanking sequence, a construct 4.8THO was created that facilitated these constructions which had a linker region with unique restriction sites positioned downstream of the TH region. Various target genes can be inserted to the unique SmaI, NruI, and SalI sites such that they will be under the transcriptional control of 4.8 kbp to +10 bp of the rat TH regulatory region. ***Transgenic*** mice express a chloramphenicol acetyltransferase reporter derived by the 4.8THO flanking sequence in a manner reflecting endogenous TH expression in all tissues tested, including discrete brain regions. Furthermore, in the olfactory bulb, there is accurate transsynaptic and developmental expression of the reporter. Human growth hormone inserted into the 4.8THO plasmid confirmed the correct targeting to catecholaminergic neurons of the CNS and in the chromaffin cells of the adrenal medulla.. Immortalized catecholaminergic neuronal cell lines employing the ***SV40*** ***T*** ***antigen*** oncogene are also generated using the 773 bp of the 5' flanking sequence of the rat TH gene. Three cell lines were established which possess a neuronal phenotype, indicated by the presence of ***neurofilament*** proteins and the absence of glial fibrillary acidic protein. Thus, ***promoter*** -driven oncogenesis in ***transgenic*** animals can be used to establish CNS cell lines from post-mitotic neurons.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5591626	A	19970107	US 1994-292926	19940818

L25 ANSWER 10 OF 11 CAPLUS COPYRIGHT 1999 ACS
TI Immortalization of neuro-endocrine cells from adrenal tumors arising in ***SV40*** T- ***transgenic*** mice

SO Oncogene (1997), 14(25), 3093-3098
CODEN: ONCNES; ISSN: 0950-9232

AU Cairns, L.A.; Crotta, S.; Minuzzo, M.; Ricciardi-Castagnoli, P.; Pozzi, L.; Ottolenghi, S.

AB Pheochromocytomas are adrenal medullary tumors which arise from the transformation of neural crest-derived cells. In the course of studies of mice ***transgenic*** for an ***SV40*** T-gene ectopically expressed in the adrenal medulla, the authors obsd. the occurrence of large, mainly bilateral tumors in a high proportion of ***transgenic*** animals. From these tumors the authors established immortalized cell lines which grow in vitro at 32.degree. (the permissive temp. for the tsA58 T-protein encoded by the transgene), but not at 38.degree.. These cells demonstrate characteristics of both neuronal (160 kDa ***neurofilament***) and endocrine (chromogranins) cells. The expression of Mash-1 and ret supports their initial characterization as early bipotential neuro-endocrine progenitors.

25 ANSWER 9 OF 11 CAPLUS COPYRIGHT 1999 ACS

TI Conditionally immortalized cell lines derived from ***transgenic*** animals and their toxicological and pharmacological uses

SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2

IN Rudland, Philip Spencer; Barraclough, Barry Roger; Kilty, Iain Charles; Davies, Barry Robert; Schmidt, Guenter

AB Provided is a cell line derived from a ***transgenic*** animal comprising (1) a conditional oncogene, transforming gene or immortalizing gene or a cell cycle affecting gene; and (2) a cell type specific ***promoter*** . They include a neuronal cell line in which the cell type specific ***promoter*** is an ***NF*** - ***L*** gene ***promoter*** , and a mammary cell line in which the cell type specific ***promoter*** is a MMTV gene ***promoter*** . The conditional oncogene, transforming gene or immortalizing gene is preferably a ***SV40*** tsA58 gene. Prodn. of ***transgenic*** Sprague Dawley rats by using mammary-targeting vector MMTVLTRtsA58U19 (contg. MMTV Long Terminal Repeat) or brain-targeting vector NF-LtsA58.delta.t (contg. human ***neurofilament*** light chain ***promoter***), and prepn. of cell lines B2LT1 and NF2C from the mammary of MMTVLTRtsA58U19 ***transgenic*** rats and the brain of NF-LtsA58.delta.t ***transgenic*** rats, resp., were shown. Prodn. of ***transgenic*** rats carrying oncogene such as c-erb.beta.-2 or transforming growth factor .alpha. (TGF.alpha.) that are highly assocd. with breast cancer was also shown. The ***transgenic*** animals and their immortalized cell lines are useful for toxicol. and pharmacol. studies.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9739117	A1	19971023	WO 1997-GB1063	19970417
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9725723	A1	19971107	AU 1997-25723	19970417
EP 904363	A1	19990331	EP 1997-917342	19970417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

L25 ANSWER 7 OF 11 CANCERLIT
TI Cell proliferation, death, and differentiation in ***transgenic*** mouse models of primitive neuroectodermal tumors induced by simian virus 40 large- ***T*** ***antigen*** .
SO Diss Abstr Int [B], (1995). Vol. 56, No. 3, pp. 1354.
ISSN: 0419-4217.
AU Fung K A
AB Human primitive neuroectodermal tumors (PNETs) are among the most common solid tumors in the pediatric age group. In addition to their histological resemblance to neural progenitors in the primitive neuroepithelium, they also express molecular markers exhibited by immature neurons and their precursor cells. In order to further understand these tumors, PNETs arising from the brain, retina and adrenal medulla in four different ***transgenic*** mouse models carrying simian virus 40-large- ***T*** ***antigen*** (***SV40*** -Tag) driven by four different ***promoters*** (ie, rat tyrosine hydroxylase ***promoter*** , human phenylethanolamine N-methyl transferase ***promoter*** , human luteinizing hormone beta-subunit ***promoter*** , and Moloney murine sarcoma virus ***promoter***) were evaluated. By studying the phenotype of these tumors, we showed that they recapitulated features of immature neurons or their progenitor cells. Thus, from the phenotypic point of view, these ***transgenic*** mouse PNETs are suitable animal models of human PNETs. Among these experimental tumors, synaptophysin was expressed universally confirming their neuroendocrine lineage, but neuronal markers (eg, ***neurofilament*** proteins) were expressed only in some tumors indicating a commitment to the neuronal lineage. These findings reflect the differences in the extent of neuronal differentiation among these experimental PNETs. The tumorigenesis and tumor progression were dissected by quantitating the rate of cell proliferation and cell death in nascent and established PNETs arising in ***transgenic*** mice carrying ***SV40*** -Tag driven by a rat tyrosine hydroxylase ***promoter*** . During initial PNET formation, a latent period of 10 weeks characterized by a low cell proliferation rate was detectable. This latent period was followed by high cell proliferation activity in the tumor cells associated with tumor progression. These findings are compatible with the hypothesis that tumor formation is a step-wise process. Interestingly, cell death in the form of apoptosis was also seen in PNETs undergoing active proliferation. This indicates that the pathway leading to apoptosis is not totally blocked during the formation of PNETs, and that efforts to induce tumor cells to undergo apoptosis will open a new chapter in cancer therapy. In summary, these studies defined several ***transgenic*** mouse PNET models as suitable experimental systems of authentic human PNETs and we used these models to study cell proliferation, differentiation, and cell death in PNET formation. (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AADAA-I9521030)

25 ANSWER 6 OF 11 CAPLUS COPYRIGHT 1999 ACS
TI Selective expression of the lacZ gene driven by the 2.3 kb ***neurofilament* light chain ***promoter*** during early neural development of ***transgenic*** mice**
SO Transgenics (1995), Volume Date 1995, 1(6), 619-28
CODEN: TADTEF
AU Le Bert, Marc; Evrard, Claudine; Gros, Francois; Rouget, Pierre
AB Several strains of ***transgenic*** mice carrying the nlslacZ sequences fused to the 2.3 kb up-stream region of the gene encoding the light form of human ***neurofilament*** proteins (NFL) were obtained. We obsd. that the transgene was expressed in various embryonic structures

of the central and peripheral nervous system. The results show that the ***promoter*** region present in the transgene provides regulatory signals involved in the onset and tissue-specificity of the NFL gene expression. However, a limited ectopic expression occurred in a few mesenchymal cells. In double- ***transgenic*** mice, carrying both the nlslacZ sequence and the polyoma large T gene under the control of the 2.3 kb ***NF*** - ***L*** ***promoter*** , the transgenes were co-integrated in tandem and coexpressed during the development of the nervous system. Proliferating cells were established in culture after dissocn. of neural structures expressing the transgenes.

L25 ANSWER 5 OF 11 SCISEARCH COPYRIGHT 1999 ISI (R)

TI MOLECULAR PHENOTYPE OF SIMIAN-VIRUS 40 LARGE ***T*** - ***ANTIGEN*** -INDUCED PRIMITIVE NEUROECTODERMAL TUMORS IN 4 DIFFERENT LINES OF ***TRANSGENIC*** MICE

SO LABORATORY INVESTIGATION, (JAN 1994) Vol. 70, No. 1, pp. 114-124. ISSN: 0023-6837.

AU FUNG K M; CHIKARAISHI D M; SURI C; THEURING F; MESSING A; ALBERT D M; LEE V M Y; TROJANOWSKI J Q (Reprint)

AB BACKGROUND: We compared the molecular phenotypes of central nervous system tumors arising in four different lines of ***transgenic*** mice (TGM) carrying the Simian virus 40 large ***T*** ***antigen*** driven by different ***promoters*** or enhancers. Two of the four lines developed primitive neuroectodermal tumors (PNETs) in the brain stem or pineal gland. A third TGM line developed retinoblastomas (a PNET-like tumor of the retina) as well as PNETs in the mesencephalon, while the fourth TGM developed retinoblastomas and adrenal pheochromocytomas. EXPERIMENTAL DESIGN: The expression of developmentally regulated polypeptides specific for the neuronal or glial lineage was examined in these PNETs using immunohistochemistry and Western blotting. RESULTS: Neoplastic cells in all of the PNETs exhibited neuronal, but no glial specific markers as evidenced by the invariable expression of synaptophysin, but no detectable glial fibrillary acidic protein or myelin basic protein. PNETs with a more differentiated neuronal phenotype expressed multiple neuronal polypeptides. The phenotypic properties of these PNETs closely resembled those found in human brain PNET biopsy samples and cell lines derived therefrom. CONCLUSIONS: We conclude that Simian virus 40 ***T*** ***antigen*** -induced PNETs in TGM exhibit the molecular phenotype of developing neurons or neuronal progenitor cells. Although many factors could influence the phenotype of these experimental PNETs (e.g., ***promoter*** , site of integration of the transgene) these PNETs appear to be suitable TGM models of human PNETs of the central nervous system.